REMARKS

Applicant respectfully requests reconsideration. Claims 1-62 were previously pending in this application. Claims 1, 6 and 31 have been amended. Support for the amendments can be found, for example, throughout the instant specification and in the originally filed claim set. Claims 22-30, 45-56, 58 and 62 have been canceled. As a result, claims 1-21, 31-44, 57 and 59-61 are pending for examination, with claims 1 and 31 being independent claims. No new matter has been added.

Rejections under 35. U.S.C. §112

Claims 1-21, 31-44 and 57-62 are rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant respectfully traverses. According to MPEP §2164.04, in order to make an enablement rejection, the Examiner has the burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971). The Examiner has not satisfied the required burden by providing a reasonable basis to question the enablement of the claimed invention and has not established a sufficient reason to doubt the objective truth of the statements provided in the instant specification.

Applicant teaches methods for the separation of half antibodies and whole antibodies, which include IgG antibodies and subclasses thereof. Although the Examiner has argued that no guidance is provided for any other mixtures of half and whole antibodies other than those containing IgG_4, this is clearly not correct. Applicant teaches on page 3, line 7, that the methods can be used to

separate, for example, IgG_1, IgG_2, IgG_3 and IgG_4 molecules. Additionally, on pages 4, 5 and 8-12, for example, methods are described that can be applied generally to half antibody and whole antibody mixtures, such as those that include the aforementioned IgG isotypes. Further, while the working example illustrates the separation of IgG_4 half and whole antibodies, it certainly does not preclude the applicability of the exemplary separation method to other IgG isotypes or the ability to perform other separation methods with the teachings provided in the instant specification in combination with the high level of skill of those in the relevant art. The Examiner is reminded that according to MPEP 2164.02, the specification need not even contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). Applicant maintains that this is the case with the disclosure provided. The disclosure provides guidance for the predictable separation of half and whole antibodies beyond merely that of IgG_4 half and whole antibodies after acidification in a glycine-HCL buffer and ion exchange chromatography, contrary to the assertion of the Examiner.

The Examiner has not adequately demonstrated why any of Applicant's teachings are incorrect or why they are not to be believed. To support the rejection, the Examiner merely contends that other immunoglobulin isotypes are not known to produce such mixtures and cites Angal et al., *Mol. Immunol.*, 30: 105, 1993. This reference, however, merely teaches that amino acid alterations in the hinge region of an IgG_4 antibody can alter biological properties of the antibody. This does not support the Examiner's contention that other immunoglobulin isotypes are not known to produce half and whole antibody mixtures. The Examiner has also argued that the specification shows that citrate buffer aggregates rather than dissociates IgG_4 half antibodies. Applicant notes, however, that contrary to the Examiner's assertion, it is shown that a glycine buffer and a citrate buffer dissociate IgG half antibodies (See, e.g., Figs. 3A-3D and 2A-2C, respectively). While the percentage of dissociation may be different between the buffers, both glycine and citrate buffers are shown to be useful for half antibody dissociation. Finally, according to the Examiner, the ability of hydrophobic interaction columns to capture and selectively release half and whole antibodies is not in evidence and one would have to experiment further with other buffers and separation means with no guidance or predictability of success. Applicant strongly disagrees. As

provided above, the specification provides adequate guidance in regard to the buffers and separation techniques that can be used in the methods of the claims (See, e.g., pages 4, 5 and 8-12), which include the use of hydrophobic columns. Additionally, the use of hydrophobic columns to perform various separations is within the skill of those in the art.

In summary, the Examiner has not adequately demonstrated that undue experimentation is required. Merely making such an assertion is not sufficient to maintain this rejection. Instead the Examiner must satisfy the burden by establishing a reasonable basis to question the enablement of the rejected claims. If the Examiner cannot do so, Applicant's asserted enablement must be accepted. Applicant maintains that with the teachings of the specification and high level of skill in the art, one of ordinary skill in certainly enabled to practice the methods of the claims.

Accordingly, withdrawal of this rejection is respectfully requested.

Claims 1-21, 31-44 and 57-62 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Applicant respectfully traverses. The Examiner has rejected claim 1 for reciting "the pH" and "the mobility", claim 9 for "the ionic strength", and claim 31 for reciting "the pH" and "the ionic strength", all of which allegedly lack antecedent basis. An antecedent recitation, however, for the aforementioned phrases in the aforementioned claims is not required as the features recited are inherent in the elements to which they refer. According to MPEP section 2173.05(e), 'Inherent components of elements recited have antecedent basis in the recitation of the components themselves. For example, the limitation "the outer surface of said sphere" would not require an antecedent recitation that the sphere has an outer surface. See Bose Corp. v. JBL, Inc., 274 F.3d 1354, 1359, 61 USPQ2d 1216, 1218-19 (Fed. Cir 2001).'

The Examiner has also rejected claims 6 and 31 for reciting "the buffer", which also allegedly lacks antecedent basis. Without conceding the correctness of the Examiner's position in this regard and in the interest of expediting prosecution of the application, Applicant has amended claims 6 and 31 to recite "a buffer" instead of "the buffer".

Further, the Examiner has rejected claims 58 and 62 for allegedly not further limiting the subject matter of the claims from which they depend, respectively. Without conceding the correctness of the Examiner's position and in the interest of expediting prosecution of the application, Applicant has canceled claims 58 and 62.

Accordingly, withdrawal of this rejection is respectfully requested.

Rejections under 35. U.S.C. §102

Claims 1-4, 10, 12-15, 20 and 21 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by King et al. (*Biochem. J.*, 281: 317, 1992).

Applicant respectfully traverses. In order for a reference to anticipate Applicant's claims, it must teach all of the limitations of the claims it is alleged to anticipate. King et al. do not provide all of the limitations of the invention of the rejected claims. For example, King et al. do not teach reducing the pH of a sample of half and whole antibodies to dissociate the half antibodies, a resulting solution that contains dissociated half antibodies and whole antibodies, and applying such resulting solution to a column. In addition, Applicant notes that King et al. provide a non-reducing SDS/PAGE analysis of a chimeric antibody showing bands at MW 150000 and MW 80000. However, when King et al. attempted to separate the bands on a column (through gel filtration HPLC), the MW 80000 could not be seen (Fig. 3). The Examiner has not demonstrated that King et al. provides the methods of Applicant's claims.

Accordingly, withdrawal of this rejection is respectfully requested.

Claims 1, 2, 5, 8, 11, 12, 15 and 20 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Paulus (U.S. Patent No. 5,292,668).

Applicant respectfully traverses. Paulus does not provide all of the limitations of the rejected claims. Paulus does not teach, for example, reducing the pH of a sample of half and whole antibodies to dissociate the half antibodies, a resulting solution that contains dissociated half antibodies and whole antibodies, and applying such resulting solution to a column.

Unlike the claimed invention, once the whole antibodies have dissociated into half-antibodies, Paulus does not reduce the pH. Paulus does propose lowering the pH at one point, but that is to create the sample of half antibodies in the first instance:

> Each sample is then subjected to conditions sufficient to break the disulfide bonds linking the F(ab') halt-molecules, but not any of the other disulfide bonds in the molecule. At the same time, these conditions are such as to prevent the formation of disulfides within a single heavy chain, for example by the addition of a dithiol complexing agent (e.g. sodium arsenite (as shown in FIGS. 11b and 11c), an aromatic arsenite such as phenylarsine oxide, or $CdCl_2$), or by modifying the conformation of the heavy chain (e.g. by lowering the pH to 4.2), or by removing all but one of the reduced cysteine residues with a proteolytic enzyme (e.g. carboxypeptidase Y). (See, e.g., column 7, lines 9-21, of Paulus).

Paulus proposes reducing the pH to prevent the formation of disulfides "within a single heavy chain." In contrast, Applicant reduces the pH to counteract a "non-covalent interaction between half antibodies":

> Nevertheless, it has been found that half antibodies non-covalently interact so as to form tetramers despite the lack of inter-heavy chain disulfide bonds. Due to this non-covalent interaction between half antibodies, their physical properties are highly similar to those of whole antibodies, making it difficult to separate half antibodies from whole antibodies under non-denaturing conditions. The current invention provides methodology to overcome this difficulty with separation. (See, e.g., page 2, lines 17-23, of the instant specification).

Because Applicant reduces the pH for a reason different than Paulus proposes, it is done at a different time. Thus, Applicant's claims recite that the pH is reduced after the sample of half

antibodies and whole antibodies has been obtained, distinguishing Paulus' proposal to reduce pH to obtain the sample of half antibodies in the first instance.

Accordingly, withdrawal of this rejection is respectfully requested.

Finally, in regard to the Examiner's statements pertaining to art made of record and not relied upon, Applicant, for the record, does not concede the correctness of the Examiner's position.

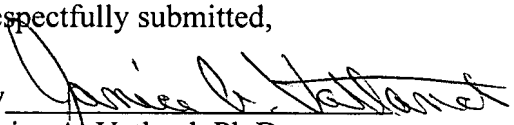
CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: May 3, 2007

Respectfully submitted,

By 

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